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Observational Study

Thromboelastography in elective total hip arthroplasty

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Abstract**BACKGROUND**

Hypercoagulability plays an important role in predisposing patients to venous thromboembolism (VTE) after total hip arthroplasty (THA). We used thromboelastography (TEG) to examine the coagulation status of patients undergoing THA.

AIM

To examine coagulation as measured by TEG in patients undergoing THA who received standard VTE chemoprophylaxis with enoxaparin.

METHODS

After ethical approval, we performed a retrospective analysis of data collected in patients undergoing primary elective THA. We analyzed TEG data on samples performed before skin incision, intraoperatively and for 5 d postoperatively. Conventional coagulation tests were performed preoperatively and on postoperative day 5.

RESULTS

Twenty patients undergoing general anesthesia and 32 patients undergoing spinal anesthesia (SA) were included. TEG demonstrated a progressively hypercoagulable state postoperatively, characterized by elevated maximum amplitude. TEG also demonstrated transient intraoperative hypercoagulability in patients receiving SA. In contrast, conventional coagulation tests were normal in all patients, pre- and postoperatively, except for an increase in plasma fibrinogen day 5 postoperatively.

CONCLUSION

Despite VTE prophylaxis, patients following total hip replacement remain in a

available from the corresponding author on reasonable request. Original data is contained on old Minitab (.mtw) files that have compatibility issues with recent versions.

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hypercoagulable state as measured by both TEG and conventional tests. This group may benefit from more optimal anticoagulation and/or additional perioperative hemostatic monitoring, *via* TEG or otherwise.

Key Words: Surgery; Orthopedic; Anesthesia; Hip arthroplasty; Hypercoagulability; Thrombelastography

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Core Tip: Patients undergoing total hip arthroplasty are a high-risk cohort for venous thromboembolism postoperatively. Thromboelastography (TEG) is a modality for investigating global coagulation status. There is limited evidence surrounding the use of TEG in this patient group. Our observational study revealed this patient cohort exhibits a progressively hypercoagulable state postoperatively, characterized primarily by elevated TEG maximum amplitude. The clinical significance of this hypercoagulability is yet to be fully elucidated, however suggests further outcome-based studies exploring anti-coagulation therapy in this cohort may be beneficial.

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INTRODUCTION

Patients undergoing total hip replacement are at high risk of developing venous thromboembolism (VTE), with Australian incidence of postoperative deep vein thrombosis (DVT) approximately 9% in this group despite VTE prophylaxis[1]. An intrinsic hypercoagulable state is thought to be a major contributor to the development of DVT in this group, as well as postoperative stasis[2-6]. Despite routine postoperative prophylaxis, VTE remains a clinically important complication of joint arthroplasty, resulting in an incidence of pulmonary embolism of 0.14%-0.27% and associated mortality rate of 19.49%[7,8]. Recent major reviews on thromboembolism in this population have demonstrated that enoxaparin is effective in reducing DVT incidence [9]. The effect of enoxaparin on the overall global coagulation picture in this group remains limited, with our data augmenting evidence provided by other small observational studies in this cohort[10].

Thromboelastography (TEG) measures whole blood coagulation and fibrinolysis. Whilst neuraxial anesthesia techniques have been reported to diminish intra- and postoperative hypercoagulability by providing improved analgesia, the incidence of VTE after total hip arthroplasty (THA) appears to be similar in patients undergoing general anesthesia (GA)[11-14]. This study aims to describe the coagulation pattern observed by TEG in patients undergoing THA, and also to determine the impact of anesthetic technique on coagulation status.

MATERIALS AND METHODS

This study is a retrospective, observational study, using data from an electronic TEG database collected between 2000-2015 at a single tertiary center. The data was originally collected as part of routine clinical care, investigating the effect of routine enoxaparin administration on postoperative coagulation in THA patients, as measured by TEG. Our primary objective was to assess coagulation status in this group as measured by TEG, comparing baseline maximum amplitude (MA) to postoperative days 1, 2 and 5. Secondary outcomes were to: (1) Assess perioperative changes in other TEG parameters; (2) Compare perioperative TEG parameter changes based on the type of anesthetic used [either GA or spinal anesthesia (SA)]; and (3) Assess perioperative changes in conventional coagulation tests (international normalized ratio, activated partial thromboplastin time and fibrinogen). This study was not designed to investi-



gate clinical outcomes or incidence of VTE.

Participants

The Austin Health Research and Ethics Committee approved a retrospective analysis of historical data. The original data was collected using TEG as routine care (approval number: LNR/19/Austin/21). The study was registered with the Australian New Zealand Clinical Trials Registry (ACTRN12619000315112).

Original participants were recruited from perioperative anesthesia and orthopedic clinics at the Austin Hospital, Melbourne, Australia. Inclusion criteria included adult patients (> 18 years) undergoing primary, elective THA with American Society of Anesthesiologists (ASA) Grade 3 or lower. Exclusion criteria included patients with significant atherosclerotic disease, known coagulopathy or thrombophilia, abnormal liver function tests, impaired renal function (estimated glomerular filtration rate < 60 mL/min/1.73m², KDIGO stage 3A or greater) and use (< 10 d pre-operatively) of any of the following medications: Warfarin, heparin (high or low molecular weight), adenosine diphosphate receptor inhibitors, glycoprotein IIB/IIIA inhibitors, adenosine re-uptake inhibitors or thromboxane inhibitors. Patients were assessed for baseline comorbidities including ischemic heart disease, cerebrovascular disease, diabetes mellitus, smoking status and hypertension.

Standardization of setting

Anesthesia was managed by a group of anesthesiologists using a standardized care protocol. All patients scheduled for surgery underwent routine pre-operative investigations in a dedicated pre-operative anesthesiology clinic. This included a multidisciplinary review by an anesthesiologist, pharmacist, peri-operative nurse and orthopedic medical officer. Investigations included electrocardiogram (EKG), Chest X-ray and pathology testing including full blood count, urea and electrolytes and coagulation studies. Comorbidities were optimized which included smoking cessation counselling, optimization of cardiovascular risk factors and perioperative anemia and glycemic control. These were managed in accordance with National Australian Guidelines. Patients were provided with full informed consent in the pre-operative anesthesiology clinic and counselled regarding anesthetic technique. Anesthesia preference was for SA unless contraindicated (previous spinal surgery, aortic stenosis, patient refusal). Routine intraoperative anesthesia monitoring included continuous EKG and pulse oximetry as well as non-invasive blood pressure monitoring, with continuous blood pressure monitoring *via* an arterial line used in select patients (*i.e.* those with cardiorespiratory comorbidities). The threshold for blood transfusion was a hemoglobin less than 8 g/dL. No patient received intraoperative fibrinolytic therapy (*e.g.* tranexamic acid). All patients received non-pharmacologic methods of VTE prophylaxis. VTE chemoprophylaxis included enoxaparin (40 mg) administered immediately prior to skin closure, continued daily until hospital discharge. Patient charts were reviewed to ascertain the incidence of postoperative VTE.

Blood sampling and processing

Blood samples for TEG measurement were taken at 6 intervals: Immediately pre-operatively (baseline), midpoint intraoperatively (mid-point of surgery), immediately prior to skin closure (end of surgery), and on postoperative days 1, 2 and 5. Blood samples for conventional laboratory coagulation tests were pre-operatively (baseline) and postoperatively on day 5. All samples were collected using a single peripheral aseptic venepuncture. Viscoelasticity was measured on a TEG5000 system (Haemonetics®, United States) performed by a technician, expert in TEG, blinded to the choice of anesthesia technique. TEG was performed within 4 min of sampling, complying with our institution's standard technique at time of collection, which has been previously reported[15,16]. TEG variables measured were reaction time (R, min), coagulation time (K, min), clot formation angle (degree), MA (mm) and fibrinolytic index (LY60%).

Postoperatively, blood for TEG and conventional laboratory coagulation assays were sampled approximately 1 h before administration of daily VTE chemoprophylaxis using standard techniques (Supplementary Appendix 1).

No patients were eliminated from this study secondary to a lack of availability of TEG.

Statistical analysis

Non-parametric statistical analysis (Friedman's test) followed by the Wilcoxon signed rank test with Bonferroni correction was used to evaluate changes in TEG over time in

each group.

The Mann-Whitney *U* test was used to compare data between patients having GA and SA. Data are presented as medians with quartiles. A $P < 0.05$ was considered statistically significant.

RESULTS

A total of 52 patients were enrolled. Indications for THA were osteoarthritis ($n = 50$) and avascular necrosis of the femoral head ($n = 2$). Thirty patients were ASA 2 and 22 patients were ASA 3. Twenty patients received GA and 32 received SA. Patients receiving GA were younger than patients receiving SA [61 years (IQR: 56-70) *vs* 74 years (IQR: 66-79), $P < 0.01$]. There were no differences in patient weight (70 kg, IQR: 65-88 *vs* 70 kg; IQR: 62-74, $P = 0.67$), sex distribution (male/female: 7/13 *vs* 14/18, $P = 0.23$), ASA class ($P = 0.56$) or incidence of cardiovascular comorbidities ($P > 0.99$) based on type of anesthetic used (Table 1). Examining the primary end-point, baseline TEG MA was within normal limits with no differences based on anesthetic technique [GA: 62 mm (IQR: 56-68), SA: 61 mm (54-65)]. MA remained within normal limits without significant difference from baseline, and without difference between anesthetic groups throughout surgery. By days 2 and 5 post operatively, MA became significantly elevated *vs* baseline, and exceeding normal limits, in both anesthetic groups (Table 2). Regarding secondary aims, we observed decreased R time, decreased K time and increased alpha angle intraoperatively *vs* baseline (Table 2). This resolved postoperatively days 1 to 5. Fibrinogen levels were elevated *vs* baseline and exceeding normal limits in both anesthetic groups postoperatively [GA pre: 3.1 (IQR: 2.9-3.3), GA post: 4.6 (4.1-5.3), SA pre: 3.1 (2.9-3.6), SA post: 4.5 (4-4.9)] (Table 3). No changes were demonstrated in other conventional coagulation tests. There were zero cases of clinically significant VTE detected within five days postoperatively. Notably one patient in the spinal cohort complained of dyspnea and chest pain three days postoperative but returned a negative Computed Tomography Pulmonary Angiography (CTPA), while one patient in the GA cohort developed unilateral calf swelling five days postoperatively before returning a negative lower limb doppler ultrasound.

DISCUSSION

Key findings

We observed that TEG findings in the THA population demonstrated a hypercoagulable state postoperatively, characterized by a steady increase in MA regardless of anesthetic technique used. Other TEG parameters demonstrated a transient, intraoperative hypercoagulability using SA, with these parameters returning to baseline by day 5 postoperatively. Fibrinogen levels were significantly elevated postoperatively, in both anesthetic groups. No difference was demonstrated in any other conventional coagulation tests compared to baseline.

Relationship with previous studies

Our findings agree with and add to previously published research. A 2013 study examining 61 patients undergoing primary, elective THA found MA increased throughout postoperative day 1, peaked by day 7, and remained elevated until day 14 [17]. Like our study, this population all received routine enoxaparin prophylaxis. This study demonstrated a decline in platelet level postoperative day 1, increase after day 3, and peak between days 7-14, and again demonstrated elevated fibrinogen level postoperative day 3 to day 14. This study examined coagulation tests on differing days to our study, measuring TEG and conventional tests immediately postoperatively, day 1, 3, 7 and 14 postoperatively [17]. Similarly, a 2014 study examining 42 patients undergoing THA, also found an increasingly hypercoagulable picture postoperatively [10]. Unlike our data, which demonstrated no difference in any TEG parameter except MA *vs* baseline, this study demonstrated the hypercoagulable picture of this patient group was mostly attributed to a mixed enzymatic and platelet contribution. Importantly however, this study examined patients on days 1, 4 and 9 postoperatively, compared to days 1, 2 and 5 postoperatively for our study. This study also used a different form of low molecular weight heparin (fraxiparine) and did not report any conventional coagulation tests, as well as enrolling fewer patients. Our findings support other small, observational study data, wherein TEG demonstrates increase in

Table 1 Baseline patient comorbidities according to anesthetic technique

	Spinal (n = 32)	GA (n = 20)	P value
Median age	74	61	< 0.01
Median weight (kg)	70	70	0.67
Sex (male)	14	7	0.23
ASA class 2	17	13	0.56
ASA class 3	15	7	
Ischemic heart disease	1	0	> 0.99
Cerebrovascular disease	0	0	
Diabetes	3	1	
Hypertension	6	4	
Smoking history	4	4	

GA: General anesthesia; ASA: American society of anesthesiologists.

Table 2 Perioperative thromboelastography findings in patients undergoing total hip arthroplasty

TEG parameter	Type	Baseline	Mid-point of surgery	End of surgery	Post-op day 1	Post-op day 2	Post-op day 5
Reaction time (R time, min)	GA	3.0 (2.6-3.6)	2.4 (1.8-3.1)	2.2 (1.8-2.4)	2.9 (2.1-3.8)	3.1 (2.3-5.0)	4.0 (2.4-5.2)
	SA	3.0 (2.7-3.8)	2.5 (1.3-3.0) ^a	2.2 (1.4-2.4) ^b	2.9 (2.3-4.1)	2.8 (2.3-3.7)	3.8 (2.7-5.7)
Clot kinetics time (K time, min)	GA	4.2 (3.6-5.1)	3.3 (2.5-4.1)	3.0 (2.8-3.4)	3.9 (2.6-5.6)	3.7 (2.7-6.4)	5.3 (3.3-7.1)
	SA	4.4 (3.8-5.1)	3.2 (2.0-4.1) ^a	2.8 (2.3-3.3) ^b	4.2 (3.2-5.8)	3.7 (2.9-5.0)	5.4 (3.9-8.0)
Clot formation angle (degrees)	GA	36 (30-43)	50 (39-58)	43 (34-53)	44 (33-54)	46 (31-58)	41 (33-50)
	SA	35 (29-40)	47 (36-57) ^b	45 (40-57) ^b	43 (28-49)	49 (37-57) ^b	36 (25-47)
Maximum amplitude (mm)	GA	62 (56-68)	68 (63-71)	65 (54-71)	71 (66-76) ^a	77 (70-81) ^b	77 (74-81) ^b
	SA	61 (54-65)	64 (59-69)	63 (58-68)	69 (66-75) ^b	74 (70-81) ^b	78 (72-82) ^b
Clot lysis (LY60%)	GA	5 (3-6)	4 (3-7)	4 (2-7)	6 (2-7)	5 (3-6)	3 (1-4)
	SA	4 (4-6)	4 (2-5)	4 (2-4)	7 (5-10) ^a	5 (4-9)	3 (2-7)

All results are presented as median with interquartile range.

^aP < 0.05.

^bP < 0.01 compared to baseline in each group.

GA: General anesthesia; SA: Spinal anesthesia; TEG: Thromboelastography; LY60%: Fibrinolysis index. (Normal reference ranges: R time: 4-9 min, K time: 1-3 min. Angle: 59-74 degrees, Maximum amplitude: 55-70 millimeters, LY60: 0%-8%)

MA post THA[18]. Intraoperative hypercoagulable states detected by TEG have been reported in previous studies and attributed to either surgical trauma or acute blood loss and hemodilution[2,3,19]. The location of hip arthroplasty surgery makes it appropriate for neuraxial anesthesia techniques (epidural and SA). It has been demonstrated neuraxial techniques may attenuate the stress response and improve local blood flow, and have been associated with direct and indirect effects on the hemostatic system[11]. A previous study reported that epidural anesthesia and analgesia attenuated postoperative hypercoagulability as measured by TEG and reduced thromboembolic sequelae post major vascular surgery[20]. However, these findings have not been reproduced[21,22]. We failed to detect an association between coagulation state and anesthetic technique used for THA. Our findings are congruent with existing evidence, which demonstrate perioperative activation of the coagulation

Table 3 Perioperative conventional coagulation test findings in patients undergoing total hip arthroplasty

Conventional coagulation test	Anesthetic type	Baseline	Post-op day 5
Prothrombin time (min)	GA	12 (12-12)	12 (11-12)
	SA	12 (12-13)	12 (12-13)
INR	GA	0.9 (0.9-1.0)	0.9 (0.9-1.0)
	SA	1.0 (0.9-1.0)	1.0 (0.9-1.0)
aPTT (sec)	GA	32 (30-35)	32 (29-35)
	SA	32 (30-34)	32 (29-34)
Fibrinogen level (g/dL)	GA	3.1 (2.9-3.3)	4.6 (4.1-5.3) ^b
	SA	3.1 (2.9-3.6)	4.5 (4.0-4.9) ^b

All results are presented as median with interquartile range.

^b $P < 0.01$ compared to baseline in each group.

GA: General anesthesia; SA: Spinal anesthesia; INR: International normalized ratio; aPTT: Activated partial thromboplastin time.

and fibrinolysis systems are similar regardless of anesthetic technique used, resulting in SA having no benefit in reducing hypercoagulability in this group[23-28]. The utility of TEG at predicting thromboembolic events in this patient population remains unknown. A comprehensive 2018 meta-analysis of 41 studies found the sensitivity and specificity of TEG at predicting thromboembolic events was 56% (95%CI: 44-67) and 76% (95%CI: 67-83), respectively[29]. This meta-analysis included data from over 10000 individuals from a heterogenous population. A prospective 2016 study focusing on the diagnostic predictive value of TEG in orthopedic patients revealed a sensitivity of 14% and specificity of 62%[30]. However, this study only performed pre-operative TEG, with several variables changing between pre-operative TEG sampling and the development of post-operative VTE limiting the interpretation of these results. To our knowledge, no evidence is currently available which examines the diagnostic predictive value of post-operative TEG at predicting VTE events in orthopedic patients. We believe our unique, novel findings add to the available evidence in this area and could help guide future outcome-based studies in this group.

Limitations

This study carried several significant limitations. It used data collected several years ago, however we feel that as anesthesia, chemoprophylaxis and surgical principles have not varied significantly *vs* when data was collected that our study results remain valid, and an important contribution to existing evidence. TEG was collected days 1, 2 and 5, compared to a single day 5 postoperative laboratory test. This was in keeping with the practice at our institution at the time of data collection. Importantly, no platelet counts were recorded for any patient during original data collection. We acknowledge that this is a major weakness in the original study design, given platelet contribution to thrombus formation, and subsequently the observed MA, and possibly the overall hypercoagulable state we observed. This is a single center, small observational study, which may limit the external validity of our findings. However, our hospital is representative of many tertiary institutions with patient outcomes equivalent to those of other tertiary hospitals in Australia[31]. The study was also observational and descriptive only and inadequately powered to assess clinical outcomes, including incidence of VTE or VTE associated complications, such as pulmonary embolism and overall morbidity/mortality. Patients were not actively investigated for venous thromboembolic complications including either the routine use of lower limb ultrasound or CTPA. However, this was never the intention of this research, and we seek to make valid data available to the broader scientific community. Ideally, further research conducted in this area would involve paired TEG and conventional coagulation tests sampling at dedicated, simultaneous time-points perioperatively, including platelet count (and ideally, platelet function).

Implications of study findings

Our findings imply that despite routine VTE chemoprophylaxis, patients undergoing THA remain in a hypercoagulable state as measured by both TEG and conventional tests. Going further, as TEG MA is a measure of thrombus size, it is influenced by both

fibrinogen and platelet number and function[32]. These are in turn both influenced by postoperative inflammatory mediators[33]. This leads us to question whether this patient group optimally anticoagulated. Existing evidence suggests solely targeting thrombin production (through administering low molecular weight heparin) may not provide sufficient protection against platelet activation, hence a hypercoagulable state may persist[34,35]. Increased TEG MA suggests that routine VTE chemoprophylaxis cannot prevent the development of platelet-dependent hypercoagulability after THA and that additional antiplatelet drugs may have a role[36,37]. A recent major review of thromboprophylaxis in major orthopedic surgery concluded that aspirin alone for VTE chemoprophylaxis is not recommended, however it's value as an adjunct remains unknown[9].

CONCLUSION

In conclusion, using TEG, we examined the coagulation status of over 50 patients undergoing elective, primary THA and found that in this patient group, TEG demonstrated a progressively hypercoagulable state postoperatively, characterized primarily by elevated MA. Hypercoagulability was also demonstrated by elevated conventional fibrinogen levels day 5 post-operatively. Our findings suggest that despite VTE prophylaxis, patients following total hip replacement remain in a hypercoagulable state as measured by both TEG and conventional tests. This group may benefit from further outcome-based studies to determine if additional perioperative hemostatic monitoring and/or anticoagulation is beneficial.

ARTICLE HIGHLIGHTS

Research background

Patients undergoing total hip arthroplasty (THA) are known to be at high risk of developing venous thromboembolism (VTE), causing significant morbidity and mortality. Thromboelastography (TEG) offers real-time information regarding the global coagulation state of a patient. This technology may be useful in investigating the coagulation of this high-risk population.

Research motivation

Available evidence surrounding the use of TEG in this patient cohort is limited, including both observational data, describing the coagulation status in these patients, and interventional data, guiding anticoagulant therapy. Our motivation for this study was to investigate the coagulation state observed in this patient group as assessed by TEG, and examine how these observations change according to time course post-operatively, and anesthetic technique, in order to ultimately improve perioperative care of these high-risk patients.

Research objectives

We aim primarily to demonstrate the coagulation profile of patients undergoing elective THA, using TEG. We secondarily aim to describe how this coagulation pattern varies according to anesthetic technique chosen [spinal neuraxial *vs* general anesthesia (GA)] and how TEG findings compare to traditional coagulation tests.

Research methods

We performed a retrospective, observational study, examining archived data of elective THA patients. Patients were selected from a dedicated orthopedic preadmission clinic, meeting strict inclusion criteria, and all received enoxaparin as routine post-operatively. We analyzed baseline TEG maximum amplitude (MA), compared to intraoperative and postoperative days 1, 2 and 5. We then compared observations based on anesthetic technique received (GA *vs* spinal) and those described by conventional coagulation tests.

Research results

We studied a total of 52 patients. We found that MA remained within normal limits, without significant difference from baseline, throughout surgery. We observed elevated MA postoperatively on days 1 and 2, before resolving day 5. This was

consistent regardless of anesthetic technique used. All patients had elevated fibrinogen levels day 5 post-operatively, with no other abnormalities detected by conventional coagulation tests.

Research conclusions

Patients undergoing elective THA demonstrate postoperative hypercoagulability when assessed by TEG (characterized by elevated TEG MA), despite routine VTE prophylaxis. Anesthetic technique (spinal *vs* GA) had no influence on the postoperative coagulation profile observed in these patients, as assessed by TEG.

Research perspectives

Our study findings imply that routine VTE prophylaxis in patients undergoing elective THA does not ablate the postoperative hypercoagulable state, according to TEG. These findings suggest that further research comparing TEG with both conventional coagulation tests, (including platelet count) and platelet function testing may be useful.

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